



# The Coming Collision of Ethics and the FDA: The Looming Problem of Cognitive Enhancement

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# The Coming Collision of Ethics and the FDA: The Looming Problem of Cognitive Enhancement

Steven Pine

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This paper is submitted as a course paper.

## Abstract

The current FDA process is not well suited for the introduction of enhancement drugs that are intended to improve certain aspects of cognition or behavior to a degree beyond what is normal. Even though there are no statutory restrictions against approving these drugs, the current positioning of the FDA approval process suggests these types of drugs would have a difficult time receiving approval for an indication that covers normal, healthy adults. However, until now the FDA has not had to confront this issue directly, since despite common media hype there is little scientific evidence that any drugs are true cognitive enhancers. That said, scientific interest in this area is growing, as is the pace of understanding about the framework of the brain. It seems only a matter of time before potentially effective cognitive enhancements are developed. Once this happens, the current FDA norm of approval for a specific indication, followed by large off-label use, could result in many important ethical and safety questions going unaddressed. Ultimately, if the FDA is going to satisfy its mission to “promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner,” a new framework will need to be developed.

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## Introduction

While humans have been seeking methods to improve their cognitive abilities for thousands of years<sup>1</sup>, the presence of drugs that have the potential to create instant improvements has never been within the grasp of science. This has made the question of how the government should regulate these drugs a largely hypothetical one up until now. Currently there is a substantial gap in Food and Drug Administration (FDA) processes for how to handle a potent enhancer when one is designed. This paper will explore this gap, and the ethical consequences it implies if not remedied. This paper will consist of three parts. In the first part, the paper will discuss what is meant by cognitive enhancers, and what the current state of enhancers is in the medical community and in popular culture. The second part will explore the approval process for a new potential enhancement drug. The third part will look at the ethical and safety issues that are unique to enhancement drugs and which are not currently within the FDA approval framework. Ultimately, this paper will conclude that a new framework needs to be explored so that these social consequences can be appropriately addressed.

## The Role of Cognitive Enhancers in Society

To get a better idea of how cognitive enhancers as a class will fit within FDA approval guidelines, it is helpful to shore up a clearer definition of what exactly constitutes a cognitive enhancer. Experts have given several different definitions to what makes up a cognitive enhancer. One definition is “prescribing medication to normal adults for the purpose of

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<sup>1</sup> For example, through language, writing, and education.

augmenting their normal cognitive or affective function.”<sup>2</sup> Another definition is “the amplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems.”<sup>3</sup> If applied to top achievers in society, this enhancement can thought to take individuals beyond the normal range of ability for the human species.<sup>4</sup>

How we define enhancement is important. One way to conceptualize enhancements are on an individual function level. For example, if a drug improves working memory, it is an enhancement. Another way is to think of enhancement on a macro level. At this level, regardless of a drugs impact of individual capacities, it is only considered an “enhancement” if it “promote[s] the flourishing of an individual and those around him.”<sup>5</sup> Some experts argue that enhancement drugs should be considered in the “same general category” of self-improvement as “education, good health habits, and information technology,”<sup>6</sup> and that “regulatory agencies should allow pharmaceutical companies to market cognitive-enhancing drugs to healthy adults provided they have supplied the necessary regulatory data for safety and efficacy.”<sup>7</sup>

Subtle definitional differences here could have significant impacts on the role government plays in regulating enhancers. For example, a broad definition of cognitive

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<sup>2</sup> Dan Larriviere et al., *Responding to Requests from Adult Patients for Neuroenhancements*, 73 NEUROLOGY 1406, 1407 (2009).

<sup>3</sup> Nick Bostrom and Anders Sandberg, *Cognitive Enhancement: Methods, Ethics, Regulatory Challenges*, 15 Sci. Eng. Ethics 311, 311 (2009).

<sup>4</sup> Torbjorn Tannsjo, *Ought we to Enhance our Cognitive Capacities?* 23 Bioethics 421, 422 (2009).

<sup>5</sup> Erik Parens, *Creativity, Gratitude, and the Enhancement Debate*, in *Neuroethics* 75, 83 (2004).

<sup>6</sup> Henry Greely, *Towards Responsible Use of Cognitive Enhancing Drugs by the Healthy*, 456 Nature 702, 702 (2008).

<sup>7</sup> *Id.* at 705.

enhancement is not limited to pharmacological intervention. Use of computers, education, training, and calculators – any sort of teaching in one sense is aimed at cognitive enhancement.<sup>8</sup> When we think of cognition as a “process an organism uses to organiz[e] information]...and use to guide behavior”<sup>9</sup> a great many activities and components of life fit this definition. For example, with the properly designed mental exercises, subjects have been shown to be able to enhance their cognitive abilities with regard to working memory.<sup>10</sup> Since enhancements cover so many categories, it may not prove to be particularly helpful to think of a single, homogenous class of “cognitive enhancers” in terms of regulation.<sup>11</sup> Instead, the specific characteristic of each drug should be analyzed to determine how it should be regulated.

This variation goes to show that there is not much consensus about how cognitive enhancers should be treated in relation to other drugs. When it comes to the FDA’s treatment of enhancers, the manner which the agency seems poised to treat them is look at the extent to which a drug is intended to bring someone to a normal state of being, or to improve them beyond normal.<sup>12</sup>

### **The Current State of Cognitive Enhancing Drugs**

Drugs currently on the market that have cognitive enhancement potential take a wide variety of forms. Some of the most well known include methylphenidate (MPH) (Ritalin) and

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<sup>8</sup> Bostrom, *supra* note 2, at 312.

<sup>9</sup> *Id.*

<sup>10</sup> Alexandra B. Morrison and Jason M. Chein, *Does Working Memory Training Work? The Promise and Challenges of Enhancing Cognition by Training Working Memory*, 18 PSYCHON BULL. REV. 46 (2011).

<sup>11</sup> Jayne C. Lucke, *Academic Doping or Viagra for the Brain?* 12 EMBO REP. 197, 200 (2011).

<sup>12</sup> See discussion in this paper, *infra*.

amphetamine salts (d-AMP) (Adderall), stimulants used primarily for the treatment of ADHD<sup>13</sup>, Modafinil (Provigil), a stimulant used primarily for treatment of several sleep disorders<sup>14</sup>, and Donepezil, used to treat Alzheimer's disease.<sup>15</sup> There are a number of other potential drugs in the research pipeline, targeting a variety of different health indications.<sup>16</sup>

There are also medical devices in use that have shown promise for cognitive enhancement. Transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS), for example, has been shown to improve performance in learning tasks by changing the excitability of the cortex of the brain.<sup>17</sup> Both TMS and tDCS directly stimulate the brain, through using localized magnetic field pulses in the case TMS and through small electrical currents through electrodes placed on the brain in the case of tDCS.<sup>18</sup> There are many fields of interest being explored by the use of TMS and tDCS, with therapeutic uses that are currently

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<sup>13</sup> M. Elizabeth Smith & Martha J. Farah, *Are Prescription Stimulants 'Smart Pills'? The Epidemiology and Cognitive Neuroscience of Prescription Stimulant Use by Normal Healthy Individuals*, PSYCHOLOGICAL BULLETIN ¶1 (2011)

<sup>14</sup> Wesensten et al., *infra* note 37, 238-247.

<sup>15</sup> Martha Farah et al., *infra* note 37, at 422.

<sup>16</sup> Tanya L. Wallace et al., *Drug Targets for Cognitive Enhancement in Neuropsychiatric Disorders*, 99 PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR 130, 130-145 (2011)

<sup>17</sup> See Bostrom *supra* note 2, at 318 (citing Hummel and Cohen, *Drivers of Brain Plasticity*, 18 CURRENT OPINION IN NEUROLOGY 667-674 (2005) (on the effects of TMS on brain plasticity); Pascual-Leone et al., *Transcranial Magnetic Stimulation and Neuroplasticity*, 37 NEUROPSYCHOLOGIA 207 (1999) (on the ability of TMS to improve performance in learning tasks).

<sup>18</sup> Jan-Hendrick Heinrichs, *The Promises and Perils of Non-Invasive Brain Stimulation*, 35 INT'L J. L. PSYCHIATRY 121, 121 (2012)



under clinical trial.<sup>19</sup> The simplicity in construction in tDCS has led to a rise of hobbyists creating do it yourself models, which raises safety concerns.<sup>20</sup>

Current and future research into cognitive enhancements touches a number of different areas. For example, cognitive enhancement may prove beneficial for individuals seeking to overcome substance abuse disorders. A number of individuals with substance abuse problems have been shown to have significant cognitive defects.<sup>21</sup> These defects often make it difficult for these individuals to execute behavioral changes needed to break their habits.<sup>22</sup> Research is progressing in using cognitive enhancers to block troubling memories in PTSD sufferers from becoming embedded and pathological, for example by preventing the emotional memories from being embedded in the amygdale.<sup>23</sup> Research is also exploring whether drugs can reverse the process once traumatic memories get embedded.<sup>24</sup> Cochlear Implants are another device that has enhancement potential. While currently cochlear implants are used to assist people without hearing, the device could also be modified and used as an enhancement by people with normal hearing by expanding the range and distance of sounds that person could hear.<sup>25</sup>

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<sup>19</sup> See *Id.*, listing more than 30 different domains of study for TMS alone, including attention, memory, and processing capabilities, among others.

<sup>20</sup> *Id.* At 122-124.

<sup>21</sup> Kathleen T. Brady, *Cognitive Enhancers in the Treatment of Substance Use Disorders: Clinical Evidence*, 99 PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR 285, 286 (2011).

<sup>22</sup> *Id.*

<sup>23</sup> Walter Glannon, *Psychopharmacology and Memory*, 32 J. MED. ETHICS 74, 74 (2006).

<sup>24</sup> *Id.* at 75.

<sup>25</sup> Henry Greely, *Law and the Revolution in Neuroscience: An Early Look at the Field*, 42 AKRON L. REV. 687, 705-706 (2009)

## Media Coverage of Cognitive Enhancing Drugs

The coverage of cognitive enhancing drugs and stories about use of such drugs has been affected by a significant amount of hype. Stories about student using drugs like Ritalin or Adderall off-label as a way to improve their studying has been a frequent topic in the news.<sup>26</sup> A recent study found that these stories were inaccurate in multiple ways.<sup>27</sup> Media coverage tended to overemphasize the benefits of cognitive enhancements compared to the risks.<sup>28</sup> Also, media reports tended to describe cognitive enhancements as something that is “common and increasing widespread,” something data about enhancement prevalence does not necessarily support.<sup>29</sup> The evidence in these stories tends to be based on anecdotal examples, rather than an appeal to scientific studies.<sup>30</sup> This unbalanced coverage has led experts to fear that the public is getting a skewed view about the realities of cognitive enhancements.<sup>31</sup>

## Scientific Studies of Cognitive Enhancing Drugs

Given this coverage in the media, questions about the prevalence and effectiveness of these drugs become especially salient. Either high prevalence or high efficacy of the drugs puts pressure on the federal government to come up with consistent standard for how to make sure these products are not on the market in an unsafe manner.

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<sup>26</sup> Partridge, *infra* note 27.

<sup>27</sup> Bradley Partridge, et al., *Smart Drugs “As Common as Coffee”: Media Hype about Neuroenhancement*, 6 PLOS ONE ¶ 4-8, Nov. 2011

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

<sup>30</sup> Cynthia Forlini and Eric Racine, *Disagreements with Implications: Diverging Discourses on the Ethics of Non-Medical Use of Methylphenidate for Performance Enhancement*, 10 BMC MED. ETHICS 9, ¶ 7-8 (2009), <http://biomedcentral.com/1472-6939/10/9>.

<sup>31</sup> *Id.* at 2.

Studies about the prevalence of use of cognitive enhancers are highly varied. For example, among student populations, studies have shown life-time illicit prescription drug use estimates range from 6.9% to 35.3%.<sup>32</sup> A study looking at how often physicians directly get requests to prescriptions for drugs they view as enhancements found that 62% of physicians received such requests at least monthly, with 12% receiving requests daily. While physicians did not always report agreeing to these requests, 37% still said that they prescribed medicine which they view as enhancement at least monthly.<sup>33</sup>

In testing efficacy, there is an overall lack of large clinical studies on the effects and safety of cognitive enhancers in healthy people.<sup>34</sup> Most of the studies that exist often have small sample sizes, are experimental, and show limited effects.<sup>35</sup> In addition there are safety concerns about the long-term effects of cognitive enhancing drugs due to this lack of research.<sup>36</sup> Cognitive enhancement is a subject that tends to receive limited research funding, partially because it is so difficult for the pharmaceutical industry to get cognitive enhancement as an indication from the FDA.<sup>37</sup>

Of the studies that have been performed to see whether various prescription medications can improve cognitive enhancement, they tend to have very small population samples, and the results are modest and mixed. Several studies have shown that the use of d-AMP or MPH

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<sup>32</sup> *Id.*

<sup>33</sup> Timothy D. Hoetzel et al., 'Doctor, Would You Prescribe a Pill to Help Me...?' *A Notional Survey of Physicians on Using Medicine for Human Enhancement*, 11 AM. J. BIOETHICS 3, 6-7 (2011).

<sup>34</sup> Larriviere, *supra* note 1, at 1409.

<sup>35</sup> Bostrom, *supra* note 2, at 313.

<sup>36</sup> William P. Cheshire, Jr. *Accelerated Thought in the Fast Lane*, 25 ETHICS AND MEDICINE 75, 77 (2009).

<sup>37</sup> Smith & Farah, *supra* note 11, at 20.

created some modest benefits in memory recall in normal individuals.<sup>38</sup> However, a number of studies also have null results, for example certain studies dealing with working memory and cognitive control.<sup>39</sup> In several studies, participants who had lower base scores were the ones most likely benefit from use of the medications.<sup>40</sup> Many research questions remained unanswered. For example, it has not been well studied whether cognitive enhancers can improve motivation in individuals. It is also not well known the extent to which enhancement has any impact on improved one's well being or happiness.<sup>41</sup> But ultimately, the evidence points to very modest benefits to healthy individuals from current drugs on the market.

## The FDA Approval Process for Cognitive Enhancers

### New Drug Approval Process

Drug is a defined term in the Federal Food, Drug, and Cosmetic Act (FDCA). An article is considered a drug under the act if it is (i) officially recognized as such by, e.g., the United States Pharmacopoeia, (ii) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or (iii) intended to affect the structure or function of the body.<sup>42</sup>

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<sup>38</sup> *Id.* at 10.

<sup>39</sup> *See Id.* at 14-17 (2011); *See also*, Wesensten et al., *Maintaining Alertness and Performance During Sleep Deprivation: Modafinil Versus Caffeine*, 159 PSYCHOPHARMACOLOGY 238-247 (2002) (Modafinil may provide no more of a cognitive benefit than caffeine does); Martha Farah, et al., *Neurocognitive Enhancement: What can we do and what should we do?* 5 Nature Rev. Neuroscience 421, 422 (2004) (“Although Donepezil, a cholinesterase inhibitor that is used to treat Alzheimer’s disease, did enhance performance in one study of healthy middle-aged pilots after flight simulator training, drug companies are looking elsewhere for pharmacological approaches to memory enhancement in normal individuals.”).

<sup>40</sup> Smith & Farah, *supra* note 11, at 17.

<sup>41</sup> Tannsjo, *supra* note 3, at 422-27.

<sup>42</sup> 21 U.S.C.A. §321(g)(1) (2009).

This separates the definition of drugs into different tracks. The first track is the track traditionally thought of – drugs designed to address a disease. But with definition (iii), the FDA clearly has a second carve-out – drugs *not* intended to diagnose, cure, mitigate, treat, or prevent a disease, but to only affect the structure and function of the body.<sup>43</sup> The structure/function track of drugs has the potential to cover an extremely broad range of products, including cognitive enhancements. Many products that we use everyday technically affect the structure of our body in some way. Courts, however, have attempted to put boundaries on what can be covered by the structure function track, so that the product must have a ‘decided’ effect upon the structure or function.<sup>44</sup> This definition should cover most potential cognitive enhancers.

Any new drug brought to the marketplace must first be approved by the FDA through a New Drug Application (NDA).<sup>45</sup> New drugs are defined as drugs not currently considered to be safe and effective for the proposed by use qualified experts in the field.<sup>46</sup> The NDA approval process is very time consuming and expensive, as of 2005 “spanning seven to twelve years and frequently costing as much as \$400 million.”<sup>47</sup> Courts have held that patients do not have any

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<sup>43</sup> See James O’Reilly, 1 Food and Drug Admin. § 13:7 (2011); “Structure or function” distinctions are a vehicle by which FDA can reach out and touch a product through its benefit claims.

<sup>44</sup> See *FTC v. Liggett & Myers Tobacco*, 108 F. Supp. 573, 576 (S.D.N.Y. 1952) (distinguishing weight loss products from cigarettes in that weight loss products “have very decided effects upon the structure of the body and the very purpose for which the product is consumed is to bring about such effects”).

<sup>45</sup> 21 U.S.C.A. §355(a). (2010) “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.”

<sup>46</sup> 21 U.S.C.A. §321(p)(1) (2009).

<sup>47</sup> Fox, *infra* note 48, 1161.

rights to purchase drugs before they are proven effective, even when the patients are suffering from dire illness.<sup>48</sup>

The NDA process only looks at approving the exact intended use claimed by the manufacturer.<sup>49</sup> However, the NDA process is not limited to drugs that have an indication to treat or cure a disease. In addition to drugs intended to treat diseases, the FDA has also approved many drugs that seek to improve “non-life-threatening, non-acute, non disease human conditions.”<sup>50</sup> For example, the FDA has approved cosmetic uses of Botox Botulinum Toxin, and has approved the height growth hormone Humatrope for use in children with short stature but no underlying disease.<sup>51</sup>

With Humatrope the approval was limited to patients at least 2.25 standard deviations below mean height.<sup>52</sup> This deviation was far enough from the mean that all parties were comfortable that it was highly unlikely that the indicated children would catch up to their peers

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<sup>48</sup> *United States v. Rutherford*, 442 U.S. 554, 551 (1979), *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470, 472 (D.C. Cir 2006), *See also* Bernstein, *infra* note 76, at 1065.

<sup>49</sup> *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1356 (Fed. Cir. 2003) (holding that “The FDA does not grant across-the-board approval to market a drug. Rather, it grants approval to make, use, and sell a drug for a specific purpose for which that drug has been demonstrated to be safe and efficacious”).

<sup>50</sup> Drew Fox, *Safety, Efficacy, and Authenticity: The Gap between Ethics and law in FDA Decisionmaking*, 2005 MICH. ST. L. REV. 1135, 1137 (Winter 2005).

<sup>51</sup> *See* Approval Memo, Botulinum Toxin Type A Product Approval Information - Licensing Action 4/12/02, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm088280.pdf> (accessed May 2<sup>nd</sup>, 2012); Medical Review for Application Number: NDA 19-640/S-003, Center For Drug Evaluation and Research, July 25, 2003, *available at*: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2003/019640\\_S033\\_HUMATROPE\\_AP.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/019640_S033_HUMATROPE_AP.pdf) (accessed May 2<sup>nd</sup>, 2012).

<sup>52</sup> Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Department of Health and Human Services; Food and Drug Administration. June 10, 2003. <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3957T1.pdf> . (Accessed May 2<sup>nd</sup>, 2012).

in height, and that their stature could have lifestyle difficulties on them.<sup>53</sup> So the Committee made it a characteristic of their chosen group's indication that treatment will only be enough to help bring them back to normal – not make them taller than average. This is similar to the diagnosis process for ADHD. The diagnosis of ADHD is on a scale basis; if a child's score on various attention questions is sufficiently below the mean then they have a clinical diagnosis and are eligible for medication to bring them back to a normal state, while individuals not below the mean are not approved for treatment in this way, even if they may benefit.<sup>54</sup>

This suggests that while manufacturers working with cognitive enhancers do not necessarily need to find a disease indication for their drug, they will have to show it is effective in bringing people to normal who have an otherwise degraded trait. This distinction points to how the FDA might be expected to approach coming cognitive enhancements. Cognitive enhancers that are aimed at normal people in trying to make them better than normal do not fall within the framework the FDA is currently working on, and so for these drugs it seems like there will be significant resistance by the agency in granting approval.

### **The Growth of Number of Diseases Indications**

If a distinction is to be drawn between enhancements from medicines intended to cure diseases, this requires an understanding of what is meant by a disease state. However, even among medical experts distinguishing between disease and non-disease states is not always easy.<sup>55</sup> The FDA defines a disease, in terms of dietary supplement claims, as either damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of

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<sup>53</sup> *Id.*

<sup>54</sup> Swanson *infra* note 127, at 742-746.

<sup>55</sup> Larriviere, *supra* note 1, at 1407.

health leading to such dysfunctioning.”<sup>56</sup> Medical dictionaries define a disease as “a definite pathological process having a characteristic set of signs and symptoms.”<sup>57</sup>

Many illnesses are defined by reaching a threshold based on having a certain number of symptoms, without a bright line distinction between a health person and an ill one.<sup>58</sup> These thresholds vary at different locations around the country. Patients will find significant differences in the types and numbers of symptoms that recognize a diagnosis of ADHD, for example, as well as difference in the frequency of stimulant medication to treat the disease.<sup>59</sup> The existence of a threshold can make distinguishing between treatment and enhancement difficult requiring separating out disorders “rooted in the body and those rooting in the mind or social norms.”<sup>60</sup> However, whether something is or is not a disease state to any individual patient will depend on that person’s “subjective experiences [and] socio-cultural values” and some feel that means the distinction has no clarity when thinking about potential enhancements.<sup>61</sup> An alternative way society could frame the question is whether a treatment can improve quality of life with benefits that outweigh the costs in terms of health risks and resource consumption.<sup>62</sup>

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<sup>56</sup> 21 C.F.R. §101.93(g)(1) (2012).

<sup>57</sup> *Dorland’s Medical Dictionary*

<sup>58</sup> Hyman, *infra* note 90, at 596 (2011).

<sup>59</sup> *Id.*

<sup>60</sup> Marc Jonathan Blitz, *Freedom of Thought for the Extended Mind: Cognitive Enhancement and the Constitution*, 2010 WISC. L. REV. 1049, 1064 (2010).

<sup>61</sup> Matthis Synofzik, *Ethically Justified, Clinically Applicable Criteria for Physician Decision-Making in Psychopharmacological Enhancement*, NEUROETHICS 89, 91 (2009). Synofzik uses as an example flight phobias.

<sup>62</sup> *Id.*



This involves an “operational definition of wellness must be in relation to the demands and goals of society, here and now.”<sup>63</sup>

With mental illness, there has been continual expansion of the number of traits that qualify as diseases under the (DSM-IVR).<sup>64</sup> In conjunction with the expansion, society has come to treat attributes that were previously considered normal – like shyness or attention deficit – as diseases deserving medication.<sup>65</sup> Without making a judgment on the positive or negative ethics associated with this expansion, the effect of the expansion is that there are a larger number of indications available for the pharmaceutical industry to latch on to. This expansion has proven profitable in many instances, such as in the treatment of depression. In the two decades after Prozac was approved, the percentage of the U.S. population receiving medication for the treatment of depression increased by greater than five times to 5% of the population.<sup>66</sup> As the disease categories continue to expand, many cognitive enhancers could seek approval under framework of these new diseases, and then see wider off-label use.

A concern is that the growth in the number of conditions considered to be diseases and the subsequent growth in medication could lead to an environment where medical intervention is seen as the only solution. This could leave out non-medicine based therapy approaches which

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<sup>63</sup> Forlini and Racine, *supra* note 28, at 9 (citing P. KRAMER, LISTENING TO PROZAC, (Penguin Books) (1997)).

<sup>64</sup> Schermer et al., *infra* note 85 (“Since the first edition of the American Psychiatric Association’s Diagnostic and Statistical Manual was published in 1952, more than four hundred new categories of mental illness have been conceived”). One recently introduced diagnosis is ‘mild cognitive impairment,’ typically used for pre-Alzheimer’s patients. No drugs have been approved for this indication yet.; *See also* Synofzik, *supra* note 59.

<sup>65</sup> Toine Pieters & Stephen Snelders, *Psychotropic Drug Use: Between Healing and Enhancing the Mind*, NEUROETHICS 63, 70 (2009)

<sup>66</sup> *Id.* at 71.

could have fewer side effects.<sup>67</sup> However, non-medical therapies are still used to help with traditional medical conditions, so they would not likely disappear.

### **How Does the FDA Determine what is an “Effective” Drug?**

The FDCA does not define what is meant by “effective,” and courts have held that the interpretation of the phrase is thus left up to the FDA to define.<sup>68</sup> The FDA considers a drug to be effective when “there is a general recognition among experts, founded on substantial evidence, that the drug in fact produces the results claimed for it under prescribed conditions.”<sup>69</sup> To be ‘effective’ is not a requirement to cure a disease as long as the treatment meets the “sponsor’s claims of prolonged life, improved physical condition, or reduced pain.”<sup>70</sup> Efficacy is shown by the manufacturer submitting “substantial evidence” that the drug “will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested.”<sup>71</sup> Substantial evidence is further defined as:

Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and

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<sup>67</sup> Schermer et al., *infra* note 85, at 82.

<sup>68</sup> *Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 154 (3d Cir. 1986); *United States v. 225 Cartons, More or Less of an Article or Drug*, 871 F.2d 409, 416 (3d Cir. 1989).

<sup>69</sup> *Rutherford*, 442 U.S. at 555.

<sup>70</sup> *Id.*

<sup>71</sup> 21 U.S.C.A. §355(d)(5)(2010).

responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed.<sup>72</sup>

The plural use of “investigations” means that at least two well-controlled studies are needed to show a drug’s effectiveness.<sup>73</sup>

The FDA has interpreted substantial evidence as requiring something than “mere statistical significance,” to instead show “clinical significance.”<sup>74</sup> Having clinical significance means that the nature of the function, in addition to existing, has to be something medically beneficial.<sup>75</sup> If a manufacturer seeks approval only on a structure function claim, and not for the treatment of a disease, they must still show that the drug has some medical benefit.<sup>76</sup> Clinical significance, on the other hand, does not mean something has to be more likely than statistical significance.<sup>77</sup> In fact, a large fraction of people who take prescription drugs are not helped by

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<sup>72</sup> 21 U.S.C.A. §355(d) (2010).

<sup>73</sup> *Warner-Lambert. v. Heckler*, 787 F.2d at 150-51.

<sup>74</sup> *Id.*

<sup>75</sup> *Id.* The purpose was so Congress could ensure that physicians had accurate information about the usefulness of drugs, something that was growing increasingly difficult given the volume of new drugs reaching the market.

<sup>76</sup> See *E.R. Squibb and Sons, Inc. v. Bowen*, 870 F.2d 678, 680-682 (D.C.C. 1989). The FDA held that in addition to having an effect indicated on a label, to be “effective” the claimed effect must have “some medical significance.” Squibb pointed to language in 21 U.S.C. 355(d) which defines substantial evidence as requiring that “the drug will have the effect it purports or is represented to have.” Squibb felt that this language mandated that the FDA approve the drug as long as it was safe and did what the label purported it did. The court disagreed, holding that Congress did not mean “to eliminate any requirement of efficacy in the sense of medical benefit” in drugs, even those only making structure function claims.

<sup>77</sup> *Id.* at 155.

them. Drugs for the treatment of Alzheimer's disease benefit only about one in three patients, and cancer drugs work for about one in four.<sup>78</sup>

### Off-Label Use of Cognitive Enhancers

Once a drug is approved for one purpose the FDA will not seek to prevent a physician from prescribing that drug for any off-label indication that the physician in her judgment sees fit.<sup>79</sup> The FDA has long held that it not involved in the practice of medicine<sup>80</sup> and Courts have affirmed that Congress' intent in the FDCA was not to "interfere with physicians' treatment of their patients."<sup>81</sup> New uses are often found after FDA approval, and Congress did not want to constrain physicians from putting existing drugs to that new use until a new indication could be approved.<sup>82</sup>

### Prevalence of Off Label Use

Studies have shown that once a drug is approved for one intended use there will be a dramatic increase in off-label sales.<sup>83</sup> Off-label use is widespread in the United States. A 2003

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<sup>78</sup> Anite Bernstein, *Enhancing Drug Effectiveness and Efficacy Through Personal Injury Litigation*, 15 J.L. & Pol'y 1051, 1076 (2007).

<sup>79</sup> See 21 U.S.C.A. §396; "Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship, See also James Beck & Elizabeth Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 76 (1998).

<sup>80</sup> See e.g. *Allergan, Inc v. Alcon Laboratories, Inc.*, 324 F.3d 1322, 1324 n.1 (Fed. Cir. 2003), *Cooper v. Smith & Nephew, Inc*, 259 F.3d 194, 197 (4th Cir. 2001).

<sup>81</sup> *United States v. Algon Chem. Inc.*, 879 F.2d 1154, 1163 (3d Cir. 1989)(citing *Chaney v. Heckler*, 718 F.2d 1174 (D.C.Cir.1983), *rev'd on other grounds*, 470 U.S. 821 (1985)).

<sup>82</sup> *Id.*

<sup>83</sup> Katherine A. Helm, *Protecting Public Health From Outside the Physician's Office: A Century of FDA Regulation From Drug Safety to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L. J. 117, 164 (2007) .

study estimated that off-label uses accounted for between 25 and 60 percent of all prescriptions in the United States.<sup>84</sup> A separate 2006 study indicated that there were more than 150 million prescriptions for off label drugs in 2001, a majority of which has little or no scientific support in regard to their safety or effectiveness.<sup>85</sup> There is a “staggering” amount of off-label use of Provigil,<sup>86</sup> with estimates as high as 90% of total prescriptions being off-label.<sup>87</sup>

Patients are often unaware when being prescribed a drug that it is being prescribed off label, or even that physicians are allowed to prescribe off-label.<sup>88</sup> Also, there is no informed consent requirement that mandates physicians tell a patient that a particular prescription is for an off-label use.<sup>89</sup> Often, the physician herself is not able to distinguish between on and off label uses.<sup>90</sup> One study found that nearly half the time physicians were unable to correctly identify the FDA status of drugs for particular indications – basically a coin flip.<sup>91</sup> In fact, most psychotropic

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<sup>84</sup> A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers’ First Amendment Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 FOOD & DRUG L.J. 439, 452 (2003).

<sup>85</sup> David C. Radley, et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCH INTERN MED. 1021, 1025 (2006).

<sup>86</sup> Fox, *supra* note 48, at 1141.

<sup>87</sup> Maartje Schermer et al., *The Future of Psychopharmacological Enhancements: Expectations and Policies*, NEUROETHICS 75, 83 (2009) (citing Vastag, B. 2004. *Poised to Challenge Need for Sleep, ‘Wakefulness Enhancer’ Rouses Concern*, JAMA 291: 167-170).

<sup>88</sup> Philip M. Rosoff & Doriane Lambelet Coleman, *The Case for Legal Regulation of Physicians’ Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 651 (2011) .

<sup>89</sup> *Id.* at 671 (citing *Blazoski v. Cook*, 787 A.2d 910, 918 (N.J. Super. Ct. App. Div. 2002)).

<sup>90</sup> See Helm, *supra* note 81, at 171 (“Because of FDA restrictions on manufacturer-sponsored physical education about off-label uses, medical professionals do not always have ready access to the necessary information about the customary use of drugs prescribed off-label.”).

<sup>91</sup> Kevin B. O’Reilly, *Physicians Know FDA-OK’d uses for Drugs Half the Time*, AMERICAN MEDICAL NEWS, Sept. 14, 2009, <http://www.ama-assn.org/amednews/2009/09/07/prsc0907.htm> (accessed May 2nd, 2012).

drugs are prescribed by generalist physicians with “little training about their effects or side effects and little time to monitor for dosage escalation.”<sup>92</sup>

The prevalence of off-label and the uninformed nature of both patient and physician creates a concern. Because off-label uses are profitable, and the costs associated with getting off-label uses formally approved may not be recoverable, drug companies may not have any motivation to continue to research a drug’s safety or efficacy once a single indication is found.<sup>93</sup> For physicians, while they do not have to fear liability from the FDA for off-label uses, “state tort law, including products liability and medical malpractice laws” can serve as a source of liability.<sup>94</sup> However, a recent article noted that there are very few medical malpractice cases dealing with the off-label prescription by a physician.<sup>95</sup>

It is not necessarily difficult for an individual to find a physician to prescribe off-label medications. The existence of a patient-doctor relationship is created based on mutual agreement between the parties, and does not depend on the existence of a disease state.<sup>96</sup> Therefore, if a patient is refused an off-label prescription by a physician, they remain free to shop other doctors until they find a physician who will provide them with the medication.<sup>97</sup> Even if physicians feel

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<sup>92</sup> Steven E. Hyman, *Cognitive Enhancement: Promises and Perils*, 69 NEURON 595, 597 (2011).

<sup>93</sup> Helm, *supra* note 81, at 166.

<sup>94</sup> *Id.* at 167-168.

<sup>95</sup> Rosoff & Coleman, *supra* note 86, at 666.

<sup>96</sup> Larriviere, *supra* note 1, at 1407.

<sup>97</sup> James J. Delaney and David P. Martin, *The Role of Physician Opinion in Human Enhancement*, 11 Am. J. of Bioethics 19, 20 (2011).

their patients may be engaging in prescription abuse, they are often not comfortable talking to their patients about that abuse.<sup>98</sup>

There is a model in place to deal with prescription standards for drugs that pose risks to patients – the Controlled Substances Act.<sup>99</sup> Certain potential cognitive enhancers, such as Modafinil, are also classified under the Controlled Substances Act. This puts an additional burden on the physician to only prescribe the drug a) for a legitimate medical purpose and b) in the course of professional practice. This begs the question of whether prescribing cognitive enhancers to healthy individuals constitutes a “legitimate medical purpose.” However, one should be skeptical about relying on the use of the Controlled Substances Act to stem the use of cognitive enhancement drugs. Both the high level of illegal drug use, as well as the extreme levels of off-label Provigil use suggest that this model would be a limited option for controlling cognitive enhancement use.

#### **Marketing Off-Label Uses**

Although off-label use is allowed, manufacturers cannot market the off-label use of their drugs. It does not matter whether statements of a company are truthful or not if their speech is intended to promote an off-label use. Any promotion is strictly liable as a violation of the Act.<sup>100</sup> It can be prosecuted even if the manufacturer had no idea they were promoting an unintended

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<sup>98</sup> Forlini and Racine, *supra* note 28, at 9 (“Data from the US National Institutes of Health shows that over 40% of healthcare providers have difficulty addressing the subject of prescription abuse with their patients”).

<sup>99</sup> Katherine Drabiak-Syed, *Physicians Prescribing “Medicine” for Enhancement: Why We Should Not and Cannot Overlook Safety Concerns*, 11 AM. J. OF BIOETHICS 17, 18 (2011).

<sup>100</sup> *United States v. Caronia*, 576 F. Supp. 2d 385, 392 (E.D.N.Y. 2008).

use.<sup>101</sup> The prevention of off-label marketing is one of the only tools available to the FDA to prevent bad behavior on the part of drug manufacturers in regard to unapproved uses.<sup>102</sup> It has been an active area of enforcement as well.<sup>103</sup> Even when manufacturers are delivering information in the form of “non-promotional speech”, those conversations have still shown to often include biased presentations.<sup>104</sup> The off-label use of enhancements “presents an inescapable conflict of interest for scientists, manufacturers, and physicians among competing incentives for consumer health on the one hand, and socioeconomic gain on the other.”<sup>105</sup>

Off-label marketing can be especially problematic when it comes to cognitive enhancement drugs. Because enhancements do not target a specific subsection of the population with a particular disease, there is the potential of immense demand for the product.<sup>106</sup> On the other hand, manufacturers have become increasingly wary of prosecution for off-label uses. Part of this fear derives from the fact that the FDA can prosecute based on what the “intended use” of

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<sup>101</sup> Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 Food & Drug L.J. 441, 442 (2009) (“The crime of shipping a misbranded or adulterated product is a strict liability crime, requiring no proof that the manufacturer knew its product were misbranded or adulterated.”<sup>9</sup> It is through these statutes that FDA regulates off-label promotion, on the theory that promoting a product for uses that are not approved creates a new intended use, making the products misbranded.”).

<sup>102</sup> See e.g. *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003).

<sup>103</sup> Mollie Hertel, *FDA’s Oversight of the Promotion of Drugs for Off-Label Uses*, 19 ALB. L.J. SCI. & TECH. 627, 631 (2009) (“Between calendar years 2003 and 2007 DOJ enforcement action resulted in 11 settlements with drug companies, which involved, at least partially, allegations of off-label promotion.”).

<sup>104</sup> Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 251 (2011) (“Disclosures relating to discussion of scientific research have a limited impact on the physician recipient, and have also been shown to give the speaker greater license to provide more biased advice than they normally would. Studies show that consumers do not interpret health-related disclaimers properly or ignore them altogether.”).

<sup>105</sup> Fox, *supra* note 48, at 1168.

<sup>106</sup> Fox, *supra* note 48, at 1170.



a product is, based on the company's "objective intent."<sup>107</sup> Based on this theory, if the manufacturer has "subjective knowledge" that product is being used primarily in an off-label way then the FDA could decide that the intended use of the drug has changed to the unapproved use, subjecting the manufacturer to liability.<sup>108</sup> Therefore, a strict reading of this law means a manufacturer would have to relabel their drug any time "the manufacturer knows, or has knowledge of facts that would lead it to know, that a device introduced into interstate commerce by the company is to be used for conditions, purposes, or uses other than those for which the company offers it."<sup>109</sup> While the FDA does not appear to be enforcing this provision against makers of current enhancement drugs, the FDA has gone after some companies under this theory, for example the makers of biliary stents.<sup>110</sup> The fact that Provigil is used up to 90% of the time off-label paints a target on this class of drugs for expanded FDA enforcement.

## **How Should the FDA Balance the Benefits and Harms of Cognitive Enhancers?**

When physicians prescribe drugs for off-label cognitive enhancing uses, it warps the typical risk benefit ratio that the agency considered. Normally this ratio is based on the benefit

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<sup>107</sup> Gentry, *supra* note 99, at 442-443 (citing 21 CFR § 801.4. "objective intent may, for example ... by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. [I]f a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put").

<sup>108</sup> *Id.*

<sup>109</sup> *Id.*, quoting Kahan, J., *Extra-Label Use*, J. MED. DEVICE & DIAG. IND. 47, 48 (Apr. 1990).

<sup>110</sup> *Id.* at 457-458 ("In March, 2007, FDA met with 20 biliary stent manufacturers and warned them about promoting their devices at vascular meetings and requested that they seek approval of the vascular indication.").

of curing a state of disease, and that can be balanced against the safety risks the drug contains. With any off-label use of a drug there is a risk that the physician or patient may not appreciate the level of risk associated with using the drug compared with the unknown benefits when using it off-label. It is often the case that drugs tested for serious diseases end up being used more and more by patients affected by less serious conditions.<sup>111</sup>

These concerns, however, are magnified in the case of a healthy individual using drugs off-label for cognitive enhancement. When using a drug off-label to attempt to cure a disease the drug was not intended for, the potential for benefit might be unknown or reduced, however the magnitude of that benefit should the drug work is still clear. With cognitive enhancements, the nature of the benefits are subtle and it is not as clear how one should balance those benefits against safety risks.<sup>112</sup> One possibility, suggested by Kesselheim, is that the FDA could allow different scaled levels of promotion of off-label uses, based on which off-label uses the FDA feels are deserving of “greater regulatory attention.”<sup>113</sup> This could allow manufacturers to participate in scholarly conferences or public medical journal articles on off-label uses without being required to begin a sNDA.<sup>114</sup> Since there is so much off-label use occurring anyways, greater participation by the manufacturers could help insure that physicians have a better understand the nature of the benefits and risks of off-label uses.

Another possibility is that the FDA could create a new category of regulation for “potential enhancement products: prescription drugs and devices with prospective or confirmed

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<sup>111</sup> Schermer et al., *supra* note 85, at 81.

<sup>112</sup> See Drabiak-Syed, *supra* note 97, at 272-74.

<sup>113</sup> Aaron S. Kesselheim, *supra* note 103, at 254.

<sup>114</sup> *Id.* at 256.

applications independent of ‘use in the diagnosis, cure, mitigation, treatment, or prevention of disease.’”<sup>115</sup> Doing so, the FDA could go beyond the typical safety and efficacy framework to also consider “individual and social values and social consequences when making approval determinations.”<sup>116</sup>

What both of these tactics having common is an appreciation that there are some individual social consequences of cognitive enhancers that are not well captured by the FDAs current approval process. The next portion of this paper will look at what some of these individual and social consequences might be.

## **Individual and Social Tradeoffs of Cognitive Enhancers**

### **Cognitive Enhancements Will Likely Involve Cognitive Tradeoffs**

Early research with cognitive enhancers suggests that their benefits are often offset by cognitive impairments in other areas. Cognitive enhancers could improve intelligence, for example, but at the same time create personality drawbacks, due to how closely cognitive and emotional processing are tied in the brain.<sup>117</sup> What has been called cognitive enhancements may often be better thought of as cognitive tradeoffs.

Take the example of memory. One current medical theory is that our memory functions such that it has “optimal levels.”<sup>118</sup> If we improve memory “storage,” we may lose effectiveness

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<sup>115</sup> Fox, *supra* note 48, at 1194.

<sup>116</sup> *Id.* at 1195.

<sup>117</sup> Drabiak-Syed, *supra* note 97, at 272.

<sup>118</sup> Glannon, *supra* note 22, at 76-77.

in memory “retrieval.”<sup>119</sup> If we take an enhancement that increases our ability to memorize long strings of numbers, we may have a hard time forming long term memories. Memories are stored in complex pathways that are still not well understood by science.<sup>120</sup> While we may know how to activate one part of the brain; and that an activation correlates to improved performance for one indication, we have a hard time figuring out which indications will be harmed by the same activation. Living evidence of the trade-offs associated with cognitive improvement can be seen in the performance of savants.<sup>121</sup> Studies have shown that an ideal amount of attention to a task requires balancing between too much and too limit focus.<sup>122</sup> A savant has too much focus on one thing, hindering attention in general. The existence of these tradeoffs suggests that “researchers need to cast a wide net” to insure that they are collecting all the data needed to balance both the benefits and the trade-offs.<sup>123</sup>

Yet, frequently the nature of these tradeoffs is unclear. For example, early evidence has suggested that the use of Adderall in individuals does not represent a tradeoff between cognitive function and creativity, as was previously suspected.<sup>124</sup>

Post-approval monitoring by the FDA also becomes more important with cognitive enhancers. The current post-approval surveillance of medicines has been criticized as “having limited effectiveness, limited stakeholder participation and a lack of transparency and

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<sup>119</sup> *Id.*

<sup>120</sup> *Id.*

<sup>121</sup> Thomas Hills and Ralph Hertwig, *Why Aren't We Smarter Already: Evolutionary Trade-Offs and Cognitive Enhancements*, CURRENT DIRECTIONS IN PSYCHOLOGICAL SCI. 373, 375-376 (2011).

<sup>122</sup> *Id.*(citing a variety of sources for this claim).

<sup>123</sup> *Id.*

<sup>124</sup> Martha J. Farah et al., *When we Enhance Cognition with Adderall, do we Sacrifice Creativity? A Preliminary Study*, 202 PSYCHOPHARMACOLOGY 541, 542 (2009).

legitimacy.”<sup>125</sup> Perhaps the FDA should consider its post-approval monitoring limitations when making decisions about the cost-benefit tradeoff of approving a drug for an indication.

### **Cognitive Enhancements Could Be Addictive**

The concern for addiction is often a focus when the media considers the impacts of cognitive enhancers. Part of the reason people today are especially suspicious about cognitive enhancers may be that currently they are mostly all forms of stimulants, which had an uncomfortable connection with illegal drug use.<sup>126</sup> Not only is there that connection, but because they are stimulants, they do have non-trivial addiction statistics. A recent study estimated that about 10% of individuals partaking in non-medical use of stimulants had become dependent on them.<sup>127</sup> More than 11 million prescription medications were thought to have been diverted to non-medical use in 2008.<sup>128</sup> Beyond stimulants, part of what can make certain drugs addictive is their ability to change the cognitive tradeoffs that one’s brain makes. Since that is a suspected problematic indication of to-be-discovered cognitive enhancers, it could give reason to be suspicious about whether future cognitive enhancers will also be addictive.

### **Cognitive Enhancement Testing Carries Troubling Consent Issues**

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<sup>125</sup> Schermer et al., *supra* note 85, at 75.

<sup>126</sup> Henry Greely, *Enhancing Brains: What are we Afraid Of?* Cerebrum, July 2010. ¶ 8  
<http://dana.org/WorkArea/showcontent.aspx?id=28792>

<sup>127</sup> James M. Swanson et al., *Contrast of Medical and Nonmedical Use of Stimulant Drugs, Basis for the Distinction, and Risk of Addiction: Comment on Smith and Farah*, 137 PSYCHOLOGICAL BULLETIN 742, 746 (2011).

<sup>128</sup> *Id.* at 744.

When someone undergoes behavioral changes when undergoing experimental cognitive therapy, the nature of their consent is affected.<sup>129</sup> Even if the patient states that they are continuing to consent as they undergo changes, there is a question of what that consent means, since the individual is under an altered state. Cognitive enhancers don't just change the thoughts that we have; they can also cause one to change their behavior.<sup>130</sup> It becomes impossible to know whether the individual would be consenting if they were in a normal state of mind, or if their consent is only a result of the behavioral change. This is especially true if a proper evaluation of drug takes an extended period of time. The concern is also heightened if the procedure produces unexpected results, which happens quite often with cognitive enhancements.<sup>131</sup>

#### **A Cognitive Enhancement Restriction is a Restriction of One's Freedom of Mind**

With any restriction regulators should be considering the balance between the risks of harm of the drug and the danger in restricting one's "freedom of thought."<sup>132</sup> Cognitive enhancement touches on a fundamental issue that is not present in many other activities limited by legislation – one's "freedom of mind."<sup>133</sup> It can be argued that using cognitive enhancement to change our brain function is an extension of a citizen's right to have "the power to make autonomous choices about the shape of self that perceives, learns, archives, and re-imagines the

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<sup>129</sup> See *Id.* at 742-46 for a discussion on this topic. The authors note that if the use of TMS and tDCS causes behavior changes while the patient is undergoing therapy, the entire nature of consent is affected.

<sup>130</sup> Blitz, *supra* note 58, at 1087-88.

<sup>131</sup> *Id.*

<sup>132</sup> *Id.* at 1114.

<sup>133</sup> *Id.* at 1116.

world.”<sup>134</sup> One way to test this argument is to consider whether we want cognitive enhancers to play in a role in helping people with moral defects to earnestly want to take medication to help themselves. Call it alcoholism, or any number of other social moral defects. Should it matter whether a morally corrupt person has a known pathological cause behind their weaknesses when deciding whether to prescribe a cognitive enhancer to his indication? If not, then that strongly suggests that a greater number of people should have access to enhancers in order to exercise control over their mind to better themselves.

### **Cognitive Enhancements Can Also Treat Existing Diseases**

If society pushes too far against medications that improve cognition, it could mean that drugs are withheld that could benefit people with actual disease conditions. After all, if medications get to the point that they can enhance normal behavior, then that means they will likely treat a number of currently out-of-reach disorders.<sup>135</sup> The current system works well for avoiding this problem in many cases. The FDA is not typically considering the likelihood of off-label uses when they are deciding whether a drug is safe and effective for a specific medical indication. Since there are a large number of specific indications available to target, pharmaceutical companies and the FDA can hone in very specific on indications as intended uses, covering a plethora of disease states.

### **Cognitive Enhancements Could Widen Societal Inequalities**

If access to cognitive enhancers is limited to a specific class of people, then an argument against allowing cognitive enhancers is that a narrow group of people could have an unfair

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<sup>134</sup> *Id.* at 1054.

<sup>135</sup> Hyman, *supra* note 90, at 597.

advantage over the rest of the populace who cannot afford or are not allowed to obtain cognitive enhancers. Cognitive enhancers could further spread the gap between the haves and have-nots. That said, it is worth noting that the default state is not a level playing field. Genetics and environmental upbringing lead to very different opportunities for education and learning.<sup>136</sup> So while the FDA might not want to exacerbate a gap, gaps in opportunities are nothing new to society. Also, access to cognitive enhancers could also have the opposite effect. If made widely and affordably available to the poor or uneducated, then these people could have a greater chance of getting ahead in society, in effect leveling the playing field.

#### **Cognitive Enhancement Could be Considered Beyond the Goals of Medicine**

The traditional goals of medicine have been expressed as including the physicians obligations to “1) prevent and diagnose disease or injury; 2) cure or treat the disease/injury; 3) reduce suffering or, if that is not possible, help patients to cope with a disease or injury; 4) educate patients about disease/injury and prognosis; 5) help patients to die in peace and with dignity; 6) reassure the “worried well” who do not have a disease/injury.”<sup>137</sup> These goals suggest that the use of enhancements might be considered to be something that is beyond the bounds of medical institutions altogether.

However, according to some modern medicine has “stripping off its traditional disease-oriented focus” and has instead moved to a doctor-patient relationship focused on improve the “subjective well-being” of a patient.<sup>138</sup> If the is the accepted framework, then it would be

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<sup>136</sup> V. Cakic, *Smart Drugs for Cognitive Enhancement: Ethical and Pragmatic Considerations in the Era of Cosmetic Neurology*, 35 J. MED. ETHICS 611, 612 (2009).

<sup>137</sup> Larriviere, *supra* note 1, at 1407.

<sup>138</sup> Synofzik, *supra* note 59, at 90.



practical for physicians to take an active role in the determining whether cognitive enhancers are something with which a patient can improve their well being.

**Cognitive Enhancement is seen by some as an Inauthentic Form of Playing ‘God’**

As one author points out, there is a paradox in thinking about using cognitive enhancers to push the limits of human bounds. On the one hand, our limitations can be considered a “fundamental aspect” of what it means to be human.<sup>139</sup> Chasing ever greater performance is a form of hubris: playing at being God.<sup>140</sup> Given the complexities of the brain, this hubris could have significant negative consequences. It can also be seen as a rejection of what humans have been given – deciding that human nature is not good enough.<sup>141</sup>

Yet on the other hand, it could also be said that it is human nature to want to constantly move beyond our limitations.<sup>142</sup> Under this frame, enhancements are less about rejecting humanity but instead embracing the most sophisticated progress that humanity has to offer. If bettering oneself through devices foreign to oneself cheapens human nature, then many of the great inventions throughout human history also cheapened human nature by their ability to move us beyond what we can accomplish with our own hands. Cognitive enhancers are drugs that have been made by man, after all.

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<sup>139</sup> Cheshire, *supra* note 34, at 76.

<sup>140</sup> Beyond Therapy: Biotechnology and the Pursuit of Happiness. Pres. Counc. On Bioethics. 285 (2003).

<sup>141</sup> *Id.*

<sup>142</sup> Cheshire, *supra* note 34, at 76.

### Cognitive Enhancement Sends a Message About Human Inadequacy

The use or diagnosis of a cognitive enhancer sends a statement about one's self. The context of the use invokes 'meaning' about an individual, even if that is not the intention. If HGH is given to a child in the desire that the child be taller, inherent within that message is that there is something wrong with them if they end up short.<sup>143</sup> Two negative messages can come out of this. First, the fact that they have to take an enhancer in the first place can invoke a feeling that one is broken. This is especially true in the case of cognitive enhancers, where a reliance on one is essentially acquiescing to the idea that some things are beyond our mental capacity to change; that one is helpless to improve without external help. Second, if an enhancer is ineffective, it can heighten the anxiety that person feels about their disability. For example, in the case of ADHD, one problem people could point to that exacerbates the disease is societies' ever growing demands on individuals to perform to the higher standard.<sup>144</sup> These concerns over our external image has led some to argue that are moving ever toward a society where a people take on a 'looking glass perspective', seeking wellness by becoming an "optimal self."<sup>145</sup> However, such a pursuit can lead to a creeping loss of one's identity. Individuals lose the ability to be an "agent of self-transformation," and are instead a "passive patient of transforming powers."<sup>146</sup> To the extent that it is limitations that give a person the contours of an identity, that identity is lost along with the limitations.<sup>147</sup>

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<sup>143</sup> Fox, *supra* note 48, at 1157.

<sup>144</sup> Schermer et al., *supra* note 85, at 82.

<sup>145</sup> Patricia D. Scripko, *Enhancement's Place in Medicine*, 36 J. MED. ETHICS 293, 294 (2010).

<sup>146</sup> Beyond Therapy: Biotechnology and the Pursuit of Happiness. Pres. Counc. On Bioethics. 285 (2003)

<sup>147</sup> *Id.*

### Cognitive Enhancement Use Can Sometimes be a Form of Cheating

Cognitive enhancement is also considered to be a form of mental cheating. While it is clear that goals are important when it comes to the enhancement debate, means to those goals are also important, and can tend to be overlooked. The manner in which goals are achieved reflects values in society that can differ depending on the type of means used.<sup>148</sup>

Parallels are drawn between steroids in sports and drugs to improve attention, memory, or motivation around exam time. However, there are distinctions between physical enhancers and cognitive enhancers. Physical enhancements are most frequently talked about in terms of their abuse in sports. However, sports are a unique type of interaction. For one, sport is governed by rules to ensure a level playing field. Once enhancements are banned in a sport, then it goes beyond a legal norm to a social norm of good sportsmanship and not trying to get an unfair advantage over an opponent. Furthermore, the value gained by sports is largely present in the competition itself – we care about how a team wins, not just that they win. In these areas society cares more about the way something is accomplished (the means), while in other areas society care more about the accomplishment itself (the goal).<sup>149</sup> Unlike a quarterback, when it comes to a surgeon we care much more whether the procedure is successful or not, and less about the methods the surgeon had to perform to obtain a successful surgery.

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<sup>148</sup> Erik Parens, *Creativity, Gratitude, and the Enhancement Debate*, in *Neuroethics* 75, 80-81 (2004). Parens also points out this can lead to status quo bias, by comparing new intervention similarities' to existing interventions.

<sup>149</sup> Synofzik, *supra* note 59, at 90.

## Cognitive Enhancement Use Can be Coercive

Coercion is another serious issue to be considered. If cognitive enhancements are allowed, then that could result in subtle or overt coercion on individuals not taking enhancement that they should take them to keep up. This is especially true in competitive situations where competitive advantages are needed in order to take a larger slice of the pie. However, there are plenty of situations in which cognitive enhancement should not be considered a zero sum calculus. For example, cognitive enhancement would likely lead to greater and faster scientific achievement.<sup>150</sup> Improvements in scientific development could be aimed at improving moral development.<sup>151</sup> Therefore, moral judgments about cognitive enhancers should take into account the purpose of the enhancement.<sup>152</sup> Whether an activity is directly competitive has an impact on how the moral perspective of cognitive enhancers should be viewed.<sup>153</sup>

## Conclusion

The current hype about cognitive enhancers largely oversells what current drugs have been shown capable of doing. However, the field is one of tremendous interest and growth, and the FDA may not have the luxury much longer of being able to avoid confronting highly effective, safe drugs that can show substantial cognitive improvement in normal individuals. Once these

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<sup>150</sup> Elizabeth Fenton, *The Perils of Failing to Enhance: a Response to Persson and Savulescu*, 36 J. MED. ETHICS 148, 150-51 (2010).

<sup>151</sup> *Id.*

<sup>152</sup> See Rob Goodman, *Cognitive Enhancement, Cheating, and Accomplishment*, 20 KENNEDY INST. OF ETHICS. J. 145, 145-158 (2010) for a discussion on the importance on distinguishing between zero-sum and non-zero sum activities and the issues of social rules surrounding activities.

<sup>153</sup> *Id.*

drugs become viable, the range of ethical dilemmas presented in this paper, among others, will land in the lap of FDA regulators trying to determine how to handle regulation of these drugs. To a certain extent, the problem may continue to be kicked down the road for a time due to the ability of pharmaceutical companies to narrowly target these drugs for some indication and then rely on off-label use. The 90% rate of off-label use of Provigil suggests that this may be the default route. However, when off-label uses become this prevalent and represent such a large percentage of a companies' profits, industry will be especially vulnerable to liability under the objective intent standard. Ultimately, the question the FDA and society has to address is whether the current system of ignoring and pretending away the reality of use will be satisfactory when the next generation of enhancement drugs rolls around. I argue that this system only heightens the safety and inequality concerns associated with cognitive enhancing drugs, and that a new framework for evaluation is the only way these concerns can be thoughtfully addressed.